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Delayed-Accelerated Hyperfractionated Radiation Therapy for Advanced-Stage or High-Risk Rhabdomyosarcoma

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The treatment of six patients with advanced-stage or high-risk rhabdomyosarcoma (RMS) is described. These patients were treated with a delayed-accelerated hyperfractionated radiation therapy (DAHFRT) regimen which delivers 5200 cGy over 20 treatment days. Acceptable early toxicity was noted when radiation therapy was given after a full course of chemotherapy and major attempts at resection of the primary tumor. The DAHFRT regimen has inherent biological and time-intensity advantages compared to other fractionation schemes which may be exploited to improve local control. The DAHFRT regimen should be considered as an alternate fractionation scheme for RMS patients and a possible foundation from which dose-escalation of radiation therapy may be attempted using advanced treatment planning technology. Late effects of high-dose radiation therapy, although a major concern, should assume less priority given the high local failure rates of advanced-stage patients and the advent of conformal radiation therapy treatment planning and delivery which can be used to reduce treatment-related toxicity. Med. Pediatr. Oncol. 29:45–50, 1997.

Key words: rhabdomyosarcoma; fractionation; pediatrics; radiation therapy

INTRODUCTION

Improving local control for advanced stage or high-risk patients with rhabdomyosarcoma (RMS) is an important objective of current treatment strategies since local failure rates remain unacceptably high. Radiation therapy is used as the primary modality or in combination with surgery to achieve local control. The optimal dosages, fractionation schedules, treatment volumes, and sequencing are undefined at present.

RMS is a radiosensitive tumor. Relative to other types of clonogenic mammalian cells, RMS is less sensitive. Because RMS has a greater capacity to accumulate and repair sublethal damage than other cells, it requires a higher minimum daily dose than other tumors which are also curable by radiotherapy. Experiments performed with transplantable RMS in an experimental rat model demonstrated the phenomenon of accelerated repopulation following treatment with radiation therapy [1,2]; cells demonstrated an increase in the rate of proliferation of surviving clonogens after cytotoxic therapy. Accelerated fractionation, contracting the total treatment time and increasing the daily dose, may compensate for tumors less radiosensitive to radiation therapy or those that undergo accelerated repopulation. Single institution and cooperative group RMS studies have not included accelerated fractionation schemes to account for these differences in relative radiosensitivity and accelerated repopulation. The experience with alternate fractionation schemes for RMS has been limited to hyperfractionation. With hyperfractionated radiation therapy (HFRT), a higher total dose may hypothetically be delivered without an increase in late effects and with only a slight increase in early effects (acute toxicity). The separation of early and late effects is achieved by maintaining the overall treatment time, increasing the total number of fractions, and delivering a smaller dose with each fraction. Several hyperfraction schemes have been tested for feasibility, toxicity, or efficacy in the treatment of advanced stage RMS [3–7]. In addition, a prospective randomized comparison of conventional (180 cGy per day to 5040 cGy) to hyperfractionated radiation therapy (110 cGy bid to 5940 cGy) is one study objective for Group III patients in the current intergroup rhabdomyosarcoma study (IRS-IV).

We recently reported our results of alternating chemotherapy and hyperfractionated radiation therapy for RMS [5,6]. Hyperfractionated radiation therapy was delivered in a split-course where patients received 150 cGy twice a day to a dose of 3000 cGy after which chemotherapy consisting of vincristine, doxorubicin, and cyclophosphamide, was given during the ensuing four week interval. This interval was followed by an additional 2400 cGy, delivered at 150 cGy twice a day, to achieve a total dose of 5400 cGy. No difference in local control was noted

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TABLE I. Clinical and Treatment Characteristics of Six Patients With Rhabdomyosarcoma Treated With Delayed-Accelerated Hyperfractionated Radiation Therapy (DAHFRT)

(Age/ Sex)	Site	Histology	Group	Treatment sequence	RT dose	Chemotherapy agents	RT toxicity	Status
16F	Retroperitoneum	Alveolar	II	SX-CT-RT-AuBMT	5200 cGy	(Me/E) × 2, (VAC/ VAdrC)-AuBMT (Me/E)	Grade 2 Skin	NED 18 mo
18M	Maxilla	Embryonal	III	BX-CT-RT	5200 cGy	(I/E) × 2, (VAC/VAdr) × 2	None	NED 12 mo
21M	Retroperitoneum	Alveolar	II	SX-CT-RT	5200 cGy	(I/E) × 2, (VAC/VAdr) × 2	None	NED 10 mo
21M	Pelvic (non-BP)	Embryonal	III	SX-CT-RT	5200 cGy	(I/E) × 2, (VAC/VAdr) × 3	Grade 4 SBO	NED 20 mo
19F	Infratemporal	Embryonal	III	BX-CT-SX-CT-RT-CT	5200 cGy	(VAdrC), (I/E)–(VAC)	Grade 2 Mucosal	TRD 12 mo
6M	Infratemporal	Embryonal	III	BX-CT-RT	5200 cGy	(I/E) × 2, (VAC/VAdrC) × 2	None	NED 20 mo

RT = radiation therapy
Me = melphalan; E = etoposide; V = vincristine; A = actinomycin-D; Adr = doxorubicin; C = cyclophosphamide; Au-BMT = autologous bone marrow rescue; I = ifosphamide
BX = biopsy; CT = chemotherapy; SX = surgery (attempted resection); non-BP = non-bladder/non-prostate
NED = no evidence of disease; mo = months after diagnosis; TRD = treatment related death; SBO = small bowel obstruction

when comparing these patients to historic controls treated with similar chemotherapy and conventionally fractionated radiation therapy (minimum dose of 5000 cGy). We postulated that the lack of difference in local control was attributable to the split-course schedule and late delivery of radiation therapy in the HFRT treatment regimen. The small difference in the calculated early (tumoral) effects and late effects of the HFRT scheme as well as the lower dose per fraction were presumed to be responsible. It is unlikely that an improvement in local control will be achieved with the current IRS-IV HFRT regimen, given the lack of significant differences in calculated early and late effects of treatment, the small dose per fraction, and the radiosensitivity and repopulation characteristics of RMS.

We designed a delayed-accelerated hyperfractionated radiation therapy (DAHFRT) treatment regimen for patients with advanced-stage or high-risk rhabdomyosarcoma considering the relevant radiosensitivity and repopulation issues and our institutional experience with HFRT. This treatment regimen, modelled after the fractionation regimens used for the treatment of epithelial tumors of the head and neck, [8] consists of a continuous course of irradiation where 180 cGy is given daily for 20 treatment days (five days per week for four weeks). During the last 10 treatment days a second daily fraction of 160 cGy is given after a 6-hour interval. The total dose is 5200 cGy.

This regimen differs from our previous experience and that of the current IRS regimen. The treatment is given in a continuous course, the overall treatment time is shortened by nearly 30%, and the relative radiosensitivity and accelerated repopulation are taken into account. The advantages, disadvantages, and future possibilities of this treatment approach will be discussed within the context of six patients who have been treated with this fractionation scheme.

MATERIALS AND METHODS

Patient Characteristics and Evaluation

Six patients with rhabdomyosarcoma were treated with DAHFRT at Memorial Sloan-Kettering Cancer Center between December 1994 and December 1995. The disease sites included were parameningeal head and neck (infratemporal fossa n = 2, paranasal sinus n = 1), retroperitoneum (n = 2), and non-bladder, non-prostate pelvis (n = 1). All patients underwent an extent of disease evaluation. None were found to have disease beyond the primary site except for one patient with intra-abdominal seeding from a pelvic primary. Two patients underwent biopsy only and the remaining four were incompletely resected. The histology of all tumors was verified at Memorial Hospital. Embryonal histology was found in four cases and alveolar histology in the remaining two. Patient characteristics and treatment details are provided in Table I.

Radiation Therapy

External beam radiation therapy was scheduled after the completion of chemotherapy in four of the six cases.

TABLE II. A Delayed-Accelerated Hypfractionated Treatment Schedule for Rhabdomyosarcoma

	Monday	Tuesday	Wednesday	Thursday	Friday	Total
Week A	180 cGy	180 cGy	180 cGy	180 cGy	180 cGy	900 cGy
Week B	180 cGy	180 cGy	180 cGy	180 cGy	180 cGy	900 cGy
Week C-am	180 cGy	180 cGy	180 cGy	180 cGy	180 cGy	900 cGy
Week C-pm	160 cGy	160 cGy	160 cGy	160 cGy	160 cGy	800 cGy
Week D-am	180 cGy	180 cGy	180 cGy	180 cGy	180 cGy	900 cGy
Week D-pm	160 cGy	160 cGy	160 cGy	160 cGy	160 cGy	800 cGy

The exceptions included a patient who received radiation therapy prior to high-dose chemotherapy and autologous bone marrow rescue and one patient who was referred for radiation therapy earlier than planned because she developed renal and hepatic insufficiency which delayed the delivery of a continuous course of chemotherapy. This patient received radiation therapy during a break in chemotherapy. In general, radiation therapy was given on day 105 of treatment. All patients were given a continuous course of radiation therapy. Treatment was given 5 days per week for 20 treatment days or 26 elapsed days. As shown in Table II, single fractions of 180 cGy were delivered during each of the first 10 treatment days. Twice-a-day treatment (hyperfractionation) was then given during the remaining 10 treatment days. The twice a day treatment included a morning fraction of 180 cGy followed 6 hours later by an afternoon fraction of 160 cGy. A total dose of 5200 cGy was prescribed to the designated target volume. One exception to the treatment scheme outlined in Table II was made for the patient with a pelvic tumor who was found to have peritoneal seeding and involvement of the omentum at laparotomy. This patient received 160 cGy to the whole-abdomen for 19 treatment days using full-thickness posterior kidney blocks. The pelvis was boosted concomitantly with 180 cGy for the last 12 treatment days to achieve a total dose of 5200 cGy.

Radiation therapy treatment planning consisted of customized patient immobilization, skin marking with tattoos, and CT scan of the primary site with the patient immobilized in the treatment position. Critical structures, tumor volumes, and treatment volumes were designed using the CT scans and by integrating data from all pre- and post-chemotherapy CT scans and MRI images. The target volume was determined by adding an appropriate margin to the tumor volume with respect to critical structures and anatomical compartments. These volumes and structures were visualized in three dimensions and targeted with a beam's eye view such that the radiation beams and subsequent isodose volumes could be shaped to provide a conformal treatment. The target volume consisted of the original tumor volume with a margin of 2–5 cm, depending on the treatment site and calculated doses to critical structures. All patients were treated on a linear accelerator with photon energies of 6 or 15 MV.

Chemotherapy

Chemotherapy agents, dosages, and schedules varied with each patient as indicated in Table I. One patient received high-dose chemotherapy with autologous bone marrow rescue after radiation therapy.

RESULTS

Clinical and Characteristics

Six patients with RMS (age 6–21 years) have received radiation therapy using the DAHFRT regimen. The distribution of sites included the head and neck, abdomen, and pelvis. All patients completed a continuous course of radiation therapy using the DAHFRT fractionation scheme after having received a partial or full course of chemotherapy, and in four cases, after a major surgical procedure.

Treatment-related Toxicity

Nearly all patients experienced a delayed skin or mucosal reaction 7–10 days following treatment. In three patients, toxicity that was at least partially attributable to radiation therapy was identified. The patient with a retroperitoneal tumor who underwent treatment with high-dose chemotherapy (melphalan and etoposide) and autologous bone marrow rescue, experienced the erythema 7–10 days following the completion of radiation therapy. With the subsequent administration of chemotherapy, this patient suffered a recall reaction and moist desquamation. The wound healed slowly in the transplant setting.

One of the patients with an infratemporal fossa tumor was initially diagnosed with Ewing's sarcoma at another institution. She received chemotherapy after initial biopsy, and later, a partial mandibulectomy with additional craniofacial resection. This attempted resection left multiple non-contiguous positive margins. After referral to our institution she received chemotherapy until renal and hepatic insufficiency occurred. At that time a decision was made to proceed with radiation therapy. Although radiation therapy was well-tolerated, her expected end of treatment mucositis was complicated by a herpes zoster infection and oral candidiasis. She was given additional chemotherapy and suffered from bacteremia and aspira-

TABLE III. Time and Dose Relationships for Different Radiation Therapy Fractionation Schemes

Schedule	Total Dose	Treatment Days	Elapsed Days	Late Effects ($\alpha/\beta = 3$)	Acute Effects ($\alpha/\beta = 10$)
Standard (180 cGy/day)	5040 cGy	28 days	38 days	80.6	59.5
Hyperfractionation (110 cGy bid)	5940 cGy	27 days	37 days	81.8	65.9
Hyperfractionation (150 cGy bid)	5400 cGy	18 days	52 days[a]	81.0	62.1
Delayed-Accelerated Hyperfractionation	5200 cGy	20 days	26 days[b]	82.1	61.0

[a]Split course alterating with chemotherapy
[b]180 cGy × 10 treatment days followed by 180 cGy + 160 cGy × 10 treatment days

tion pneumonia. She died of respiratory failure one month after completing radiation therapy.

The patient with a pelvic tumor who was treated with a modification of the DAHFRT regimen, tolerated treatment without complications but suffered a small bowel obstruction eight months after radiation therapy. This patient had originally presented with extensive intra-abdominal disease and had undergone major surgery prior to chemotherapy and radiation therapy. The initial surgery consisted of a laparotomy with debulking of the primary site and resection of sites of omental and peritoneal implants. At that time all samples of ascitic fluid were found to contain malignant cells. The patient successfully completed a planned regimen of chemotherapy followed by consolidative radiation therapy. Seven months after completing radiation therapy the patient developed signs and symptoms of small bowel obstruction. An exploratory laparotomy was performed where adhesions were lysed, and a portion of the small bowel was resected. No evidence of disease was found at the time of exploration or following the pathologic review of the operative specimens.

DISCUSSION

The late effects of radiation therapy depend primarily on fraction size; the early (acute or tumoral) effects depend on fraction size and overall treatment time. Hyperfractionated radiation therapy, in its most common form using a smaller dose per fraction and similar overall treatment time, has been selected as an alternative to conventionally fractionated radiation therapy in an effort to improve local control and avoid late effects. Early and late effects are separated by splitting the total dose into smaller fraction sizes while maintaining the overall treatment time. When hyperfractionated treatment is given, the total dose must be increased since the dose per fraction is reduced. Thus, a higher total dose is delivered to hypothetically enhance tumor control without an increase in late effects.

Our institutional experience with hyperfractionated radiation therapy for RMS did not demonstrate a benefit for hyperfractionation in terms of local control [5,6]. In retrospect, it was unlikely to demonstrate a difference in local control even though the dose per fraction (150 cGy) was slightly larger than that used in other HFRT regimens and the total dose was increased from 5000 cGy to 5400 cGy [4]. Without a reduction in overall treatment time and an incremental increase in daily dose, hyperfractionated radiation therapy does not address the problem of accelerated repopulation of surviving tumor clonogens. Furthermore, the small fraction size (110 cGy) of most hyperfractionation regimens, may not be sufficient to address differences in the radiosensitivity of RMS compared to other mammalian tumor cells.

Comparing Fractionation Schemes

Four fractionation schemes are listed in Table III along with their corresponding number of treatment days, overall treatment time and calculated biologically equivalent doses based on the assumptions of the linear-quadratic formula [9]. Tumor is considered an early responding tissue in the linear-quadratic model; efforts to improve local control should be directed at enhancing early effects. Increasing the dose per fraction increases the likelihood of early effects; early effects also depend on overall treatment time. In the simplest form, the linear-quadratic formula does not account for differences in overall treatment time. Thus, the probability that one regimen will increase local control when compared to another requires a comparison of biologically equivalent doses and a separate assessment of the differences in overall treatment time. Comparing alternate fractionation schemes with conventionally fractionated radiation therapy (180 cGy per day to 5040 cGy), we find that the IRS-IV HFRT regimen has a similar number of treatment days, overall treatment time, and late effects with a 10% increase in early effects. With the MSKCC HFRT split-course regimen, the 30% reduction in the number of treatment days is offset by the 20% increase in overall treatment time. The calculated late effects are similar and there is only a slight (6%) increase in early effects. Finally, comparing the delayed-accelerated treatment regimen to the conventionally fractionated treatment regimen shows a 30% reduction in the number of treatment days and overall treatment time. There is a 4–6% increase in both early and late effects.

The delayed-accelerated hyperfractionated radiation

therapy regimen has a biological dose advantage and a time-intensity advantage when compared to conventional and hyperfractionated regimens. These benefits may be further augmented by escalating the total dose delivered in the DAHFRT regimen. The total dose recommended for microscopic versus macroscopic disease and recommended treatment volumes are currently under review.

Optimal Dose of Radiation Therapy

For high-risk patients with RMS the optimal dose of radiation therapy is not established. Historically, local control rates of 90% have been achieved with doses of 55–65 Gy given with conventional fractionation. With the advent of effective chemotherapy, investigators have focused on eliminating radiation therapy or reducing the total dose in an effort to limit the potential late effects of treatment. Radiation therapy data from the IRS trials do not identify the optimal doses of radiation therapy which should be used in the treatment of high-risk patients. IRS-I found a trend for decreasing local control in patients treated with less than 40 Gy and for tumors measuring greater than 6 cm. The local recurrence rate was 32% for doses < 40 Gy and 12% for doses > 40 Gy ($p < 0.41$) [10]. In IRS-II, doses were prescribed according to tumor size and age in patients receiving vincristine, actinomycin-D, and cyclophosphamide (VAC) chemotherapy: 45–50 Gy for tumors < 5 cm, 50–55 Gy for tumors $\geqslant$ 5 cm and a 10% reduction for ages < 6 years. The local failure rates were 10% in group II, 30% in group III, 41% in group IV, 34% for tumors > 5 cm, and 23% for tumors < 5 cm. Local control was poor in group III and IV patients even though they received chemotherapy and 50–55 Gy [11]. Jereb and others [12] reported on 59 patients with incompletely or unresectable embryonal RMS who received VAC based chemotherapy and radiation therapy doses of 45–50 Gy over a protracted period of 5–8 weeks. They achieved local control rates of 94% for patients with microscopic disease treated with 30–49 Gy and local control rates of 85% for patients with gross disease treated with doses in excess of 50 Gy. More recent data from the IRS-III trial [13] demonstrated no significant improvement in local control and a progression-free survival at 5 years of 55% (Group II) and 61% (Group III).

The aforementioned reports characterize radiation therapy carried out with conventional fractionation. In an effort to improve local control and minimize the late effects due to radiation therapy, alternating chemotherapy with hyperfractionated radiation therapy (150 cGy twice a day to 45 or 54 Gy) has been investigated at our institution. The first report on this alternative fractionation scheme described overall local control rates of 83% and survival of 58% for 12 patients at median follow-up of 25 months [4]. With further accrual of 67 patients and with a median follow-up of 55 months in this study, the progression free survival was 87% in group II patients and 57% in group III patients. HFRT was studied in 14 patients by Regine et al. [7], They reported 75% absolute continuous control at 2 years in patients with gross disease after induction chemotherapy.

Balancing Early and Late Effects

While reducing late effects is important for patients with early stage disease or those with a high probability of local control, late effects should assume less of a priority if the possibility of local failure remains high and the effects of recurrence include significant morbidity and overwhelming mortality. The long-term toxicity of systemic chemotherapy aside, the fundamental approach for reducing late effects has been to reduce the dose per fraction and the total dose of radiation therapy. This approach contradicts what we know about the radiobiology of RMS. Hyperfractionated radiation therapy and delayed-accelerated hyperfractionated radiation therapy both result in acute toxicity which is tolerable and manageable. Our current limitations with alternate fractionation schemes have been defined by our decision to select a total dose that will achieve a similar isoeffect with regard to late effects. It is plausible to attempt to improve local control by escalating the total dose using conformal treatment technology without a concomitant increase in early and late effects.

The Benefit of Conformal Therapy When Acute or Late Toxicity May Be a Problem

Conformal radiation therapy treatment planning and delivery technology, as a complement to alternate fractionation schemes, can be used to improve local control and reduce the acute and late toxicity of radiation therapy. This impression is based on the premise that conformal treatment technology will permit the delivery of high-dose radiation therapy or the escalation of radiation therapy doses with a simultaneous reduction in the dose to normal tissues. Conformal treatment technology will not impede the intensification of chemotherapy and will likely reduce early and late effects by treating nontarget volume tissues to a significantly lower dose.

The benefit of conformal technology was observed for patients treated with the DAHFRT regimen. Without exception, the toxicity of the head and neck treatment would have been greater without the use of multiple noncoplanar beams to spread out the dose to normal tissues. In comparison, the skin dose received by one patient who had parallel opposed portals was higher than that received by the head and neck patients. The intensity of the erythema 7–10 days following the treatment, although tolerable, was more severe. The hallmark of conformal technology is the ability to design radiation beams that traverse normal tissues with the least susceptibility to early and late effects of treatment. Also, increasing the

number of beams, and thereby spreading out the dose to normal tissues, reduces the overall potential for toxicity.

Summary

Alternate fractionation schemes require further investigation to secure radiobiological evidence of their advantages. Delayed-accelerated hyperfractionated radiation therapy should be considered for its time-intensity characteristics. The evidence indicates that it is tolerable and leads to no significant increase in early or late toxicity when careful treatment planning is performed. The optimal total dose is an important unknown and should be sought by escalating the total dose of alternate fractionation schemes and by taking advantage of conformal treatment planning and delivery technology which is now widely available.

REFERENCES

1. Broerse JJ and Barendsen GW. Relative biological effectiveness of fast neutrons for effects on normal tissues. Curr Top Radiat Res Q 8:305–350, 1973.
2. Hermens AF and Barendsen GW. Changes of cell proliferation characteristics in a rat rhabdomyosarcoma before and after x-irradiation. Eur J Cancer 5:173–189, 1969.
3. Donaldson S, Asmar L, Fryer C, Wharam M, Breneman J, Gehan E, and Maurer H. A hyperfractionated radiation protocol to improve local control without increasing late effects in childhood rhabdomyosarcoma. Med Pediatr Oncol 23:188, 1994.
4. Mandell LR, Ghavimi F, Exelby P, and Fuks Z. Preliminary results of alternating combination chemotherapy (CT) and hyperfractionated radiotherapy (HART) in advanced rhabdomyosarcoma (RMS). Int J Radiat Oncol Biol Phys 15:197–203, 1988.
5. Merchant TE, Ghavimi F, and Cahill J. Results of alternating chemotherapy and hyperfractionated radiation therapy in childhood rhabdomyosarcoma. Radiology 197 (P):224, 1995.
6. Merchant TE, Ghavimi F, and Cahill J. Results of alternating chemotherapy and hyperfractionated radiation therapy in childhood rhabdomyosarcoma. Submitted for publication 1997.
7. Regine WF, Fontanesi J, Kumar P, Zeitzer K, Greenwald C, Bowman L, Shapiro DN, Rao BN, Kun LE. A phase II trial evaluating selective use of altered radiation dose and fractionation in patients with unresectable rhabdomyosarcoma. Int J Radiat Oncol Biol Phys 31:799–805, 1995.
8. Fu KK, Clery M, Ang KK, Byhardt RW, Maor MH, Beitler JJ. Randomized phase I/II trial of two variants of accelerated fractionated radiotherapy regimens for advanced head and neck cancer: Results of RTOG 88–09. Int J Radiat Oncol Biol Phys 32: 589–597, 1995.
9. Fowler JF. The linear-quadratic formula and progress in fractionated radiotherapy. Br J Radiol 62:679–694, 1989.
10. Tefft M, Lindberg RD, and Gehan EA. Radiation therapy combined with systemic chemotherapy of rhabdomyosarcoma in children: Local control in patients enrolled in the intergroup rhabdomyosarcoma study. NCI monograph 56:75, 1981.
11. Tefft M, Wharam M, Gehan E. Local and regional control by radiation of rhabdomyosarcoma in IRS II. Int J Radiat Oncol Biol Phys 15 (S1):159, 1988.
12. Jereb B, Ghavimi F, Exelby P, and Zang E. Local control of embryonal rhabdomyosarcoma in children by radiation therapy when combined with chemotherapy. Int J Radiat Oncol Biol Phys 6:827–833, 1980.
13. Crist W, Gehan EA, Ragab AH, et al. The third intergroup rhabdomyosarcoma study. J Clin Oncol 13:610–630, 1995.